REMARKS

Claims 1-32 are pending. Applicants thank the Examiner for withdrawing in part objections to the specification and certain rejections, as described at page 3 of the instant Office Action.

Please cancel claims 13-15, 20-21, and 27-32 without prejudice, because they were withdrawn from consideration as a result of restriction requirement. Applicants reserve the right to further prosecute the subject matter of these claims in the future in a continuing or divisional application. Upon entry of the amendment, claims 1-12, 16-19, and 24-26 will be pending. Applicants respectfully request reconsideration in view of the amendments and remarks made herein. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Objection to the Specification

The Examiner objected to the specification because the Examiner alleges that the status of the patent applications referenced throughout the disclosure must be updated. Applicants respectfully request that the Examiner provide the basis for this objection. Applicants are aware of 37 CFR 1.78(a)(2) and (5), but the rules pertain only to applications referenced for the purpose of priority claims. Accordingly, these rules do not provide basis for the objection in the instant Office Action, which is directed to paragraphs throughout the specification other than the paragraph captioned Reference to Related Applications, for example, in Background of Invention. If the Examiner can provide the basis for the request, Applicants will consider amending the specification accordingly.

Objection to the Claims

The Examiner objects to claims 8-9, 16-17, 19, and 26 as allegedly reciting non-elected species. In response, Applicants respectfully point out that these claims all recite Markush-type groups, which include an elected species as well as non-elected species. Election of species is for search purposes only. Applicants are not required, at this point in time, to amend claims to exclude all non-elected claims. Applicants respectfully direct the Examiner's attention to MPEP 803.02, which states:

> The provisional election will be given effect in the event that the Markush-type claim should be found not allowable. Following election, the Markush-type claim will be examined fully with respect to the elected species and further to the extent necessary to determine patentability. If the Markush-type claim is not allowable over the prior art, examination will be limited to the Markush-type claim and claims to the elected species, with claims drawn to species patentably distinct from the elected species held withdrawn from further consideration.
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> On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a non-elected species, the Markush-type claim shall be rejected and claims to the non-elected species held withdrawn from further consideration.

As stated by the Examiner in the Office Action dated December 18, 2001, upon allowance of a generic claim, Applicants will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 C.F.R. 1.141. Accordingly, Applicants submit that no amendment is necessary at this time.

35 USC §112, first paragraph - enablement

The Examiner rejected claims 1-12, 16-19, and 22-26 as not enabled. The Examiner acknowledged that the claims are enabled for a method of reducing dendritic retraction *in vitro* induced by leukemia inhibitory factor (LIF) or ciliary neurotrophic factor (CNTF), and for a method of reducing the inhibitory effects of LIF *in vitro* on OP-1 stimulated dendritic growth, by using an antibody or PI-PLC. The Examiner, however, alleged that the specification is not enabling for a method of administering all possible molecules to a mammal that potentiate morphogen activity, promote neuronal cell growth, treat a disorder characterized by neuronal cell loss, or treat a neurodegenerative disorder.

Applicants hereby submit that the specification adequately enables the complete scope of the invention as claimed. When claiming a genus, Applicants need only provide sufficient description of a representative number of species. MPEP 2163. Further, for a claimed genus, representative examples together with a statement applicable to the genus as whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the

information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. MPEP 2164.02. As described below, Applicants submit that the examples below, showing various compounds that relieve the inhibition of OP-1, thereby potentiating the OP-1 induced growth of neuronal cells, provide sufficient guidance to enable the practice of the claimed invention as a whole.

The specification describes an antibody to gp130, which can be used to reduce the LIF-induced dendritic retraction. The specification also describes PI-PLC pretreatment reduced CNTF-induced dendritic retraction. Further, Applicants described how cAMP can inhibit dendritic growth (Figures 8A and 8B of the specification), and therefore, it is reasonable that blocking the effect of cAMP can release such inhibition. Applicants identified protein kinase A inhibitor H89 ((2-p-bromocynnamylaminoethyl)-5-isoquinolinesulfonamide) and sterically constrained enantiomers of cAMP and of dibutyl cAMP as drugs that interfere with cAMP signaling. See Example 1.3 on page 31 of the application. These compounds, among others, are well known in the art as efficient inhibitors of protein kinase A that block cAMP-dependent activation of kinase A. See, for example, Exhibit A and the references cited therein. Based on these data and the disclosure of H89 and other protein kinase A inhibitors, one skilled in the art would have thought and been able to use these inhibitors to counter dendritic growth inhibition by cAMP.

In addition, it has been shown that at least four molecules, namely small molecules PD98059 and U0126 and two dominant negative forms of MEK1 and ERK2 protein kinases, overcome morphogen inhibition and enhance growth stimulation by a morphogen OP-1. PD98059 and U0126 are structurally unrelated and are not amino acid-based, whereas the dominant negative forms of MEK1 and ERK2 are proteins. These data are described in the attached manuscript (Exhibit B). See Abstract at page 3 for the summary. All four molecules possess one or more of the characteristics described in the specification in Example 2 (page 31, lines 14-23 of the specification) and are evaluated by a method essentially as described in Example 3.1 of the specification. PD98059, U0126, and dominant negative forms of MEK1 and ERK2 represent very diverse molecules, structurally completely different from each other and from the example described in the specification, namely an antibody against gp130.

Therefore, Applicants now have provided multiple, very diverse molecules that have been shown to relieve OP-1 inhibition, thereby enabling the practice of the claimed invention. Applicants submit that these results amply demonstrate that Applicants' disclosures in the instant application fully enable practicing the invention.

The Examiner also contends that the specification does not enable treatment of neurodegenerative diseases. The Examiner states that the specification does not teach any methods or working examples that administer any molecule to a mammal to overcome morphogen inhibition. Applicants respectfully traverse this characterization. As the Examiner acknowledged in the Office Action dated November 13, 2002, pages 22-24 of the specification outlines a procedure for administering to a mammal a molecule capable of releasing inhibition on morphogen activity. The specification describes various routes of administration and formulation for such administration. An example of a carrier is given (physiologic saline), as well as the general description of an acceptable carrier or vehicle. An example of interval of administration is given, *i.e.* continually by intravenous or intraperitoneal administration or periodically by injection. Also at line 10 of page 23, a published PCT application WO 94/03600 is referred to as describing soluble complex form of morphogenic proteins, including how to make, test and use them, providing the details of the administration of a morphogen to be combined in the instant specification. For example, a soluble morphogen may be provided in a physiological buffer at the concentration of 0.001% to 10% w/v, typical dose ranges are 10 ng/kg to 1g/kg body weight, preferably 0.1 μg/kg to 100 mg/kg body weight. Such doses are safe in growing rats when administered daily for 21 consecutive days, and in neonatal mice when injected for 10 consecutive days (page 59, lines 18-31). It is implicitly understood by one skilled in the art that the duration of administration of any medicament is until the symptom improves, the medicament is no longer tolerated by the patient, or no improvement based on the administration of the medicament is seen.

The Examiner is questioning whether the *in vitro* experiments presented in the application are predictive of success *in vivo*. Applicants submit that for this particular application, this general observation is not applicable and the *in vitro* data described by Applicants are useful in assisting one skilled in the art for the routine determination of the details of administration of the medicament.

Applicants submit that the following *in vivo* data show that Applicants' observations *in vitro* are in good correlation with *in vivo* data, indicating the *in vitro* conditions used in Applicants' experiments reflect *in vivo* conditions. To begin with, Snider had previously observed that nerve growth factor stimulated dendritic growth *in vivo* (Snider (1988) *J. Neurosci.* 8(7):2828-2834, see Materials and Methods and Figures 1 through 3)(Exhibit C). Applicants showed *in vitro* dendritic growth was stimulated by nerve growth factor (See Lein *et al.* (1995) *Neuron* 15:597-605, Figure 4, also the paragraph bridging pages 600-601)(Exhibit D). Accordingly, this establishing the basis for an *in vitro* system of examining an *in vivo* phenomenon of dendritic growth. Using this *in vitro* system, Applicants showed nerve cell growth stimulation *in vitro* by OP-1, as described in the specification and in Lein *et al.* (1995) *Neuron* 15:597-605, see page 601. Subsequently, Granholm *et al.* (1999) *Cell Transplantation* 8(1): 75-85 (Exhibit E) showed that OP-1 stimulates nerve cell growth *in vivo* (See Abstract on page 75, MATERIALS AND METHODS on page 76, and RESULTS on page 77). Further, Applicants showed that LIF inhibits dendritic growth *in vitro*, as described in the examples in the instant specification and in Guo *et al.* (1999) *J. Neurosci.* 19: 2113-2121, page 2114, and Figures (Exhibit F). Subsequently, Morikawa *et al.* (2000) *Neuroscience* 100(4): 841-848 (Exhibit G) showed evidence that LIF inhibits dendritic growth *in vivo* (See page 842 for Injection of cells and page 843 for the results). All these data validate the *in vitro* model described in the specification as predictive of *in vivo* behavior of cells and compounds.

The Examiner cites three exemplary articles, Halliday *et al.*, Steece-Collier *et al.*, and Feigin *et al.* to demonstrate her point of unpredictability in the art regarding Alzheimer's disease, Parkinson's disease, and Huntington's disease, which the Examiner characterizes as recalcitrant to treatment in the art. Applicants respectfully disagree with the Examiner's interpretation of the cited articles.

Halliday *et al.* is a review of the literature on events contributing to the formation of senile plaques and the treatments to ameliorate this pathology and its clinical consequences. Much of the discussion is devoted to the observed inflammatory symptoms and effects of anti-inflammatory drugs, and there is no discussion at all about the neuronal cell death or replenishment of neurons. Applicants' claimed invention relates to enhancing neuronal cell growth to compensate for the neuronal cell death and degeneration. Halliday *et al.* concerns the

events that lead up to the neuronal cell death. Applicants submit that Halliday *et al.* is inapposite to the validity of the treatments claimed in the instant application.

Steece-Collier *et al.* is a commentary on an accompanying paper by Dauer *et al.* published in the same issue of the journal, which reported on α-synuclein's role by showing how knockout mice lacking α-synuclein are resistant to chemically induced Parkinson's disease. Steece-Collier *et al.* makes no statement about Parkinson's disease being recalcitrant to treatment in the art. In fact, in the first paragraph of the article, the authors state that there are several treatments that are effective for a number of years. The shortcomings of these treatments, according to the authors, are that their usefulness wanes over time and they are accompanied by unacceptable side effects, and not that these treatments are ineffective. The article then goes on to discuss how Dauer *et al.* conclusively showed that the disruption of the α-synuclein gene confers specific resistance to degeneration of dopaminergic neurons and the critical role of α-synuclein in such degeneration. Applicants submit that Steece-Collier *et al.* is in accord with Applicants' claimed invention by indicating counteracting neuronal degeneration would prevent manifestation of Parkinson's disease.

Feigin *et al.* discusses various aspects of Huntington's disease and the ongoing research for effective treatments. On page 486 under the heading Experimental therapeutics, there are twelve animal studies cited as promising, and one human study cited as safe and well tolerated. Only one human study is cited as having failed to demonstrate neuroprotective effect despite positive results from animal studies. Contrary to the Examiner's assertion, Feigin *et al.* does not show that the results of human clinical trials are unpredictable. Instead, it cites numerous successful studies which tested compounds for treatments based on the understanding of the mechanisms of the disease. Feigin *et al.* also makes no mention of neuronal cell death or replenishment of neurons.

The Examiner further cites other articles to support her contention that the state of the art is such that it is hard to predict clinical results from *in vitro* studies. The Examiner cites Lo to allege that the state of the art does not yet allow translation of successful *in vitro* results directly into the clinic. Lo's discussion, however, is primarily about the correlation of genetic markers and/or expression levels of proteins with a disease. The article points out that the major

technical challenges are throughput and genetic manipulation (page 29). Applicants' claimed invention is based on a distinct biochemical and physiological observation that a morphogen such as OP-1 enhances neuronal cell growth and differentiation, and that there exist factors that dampen that effect, and not mere observations of possible correlations of concurrent phenomena. In addition, as indicated above, Applicants have shown adequate correlations between the *in vitro* effectiveness of the claimed invention and *in vivo* results, which involves analysis of the actual CNS tissues. The neurons used in Applicants' *in vitro* experiments are primary culture neurons isolated from brains, and not cell lines, making the *in vitro* experiments relevant for applications *in vivo*. Lo advocates using live animal brain slices, an *ex vivo* model for the actual brain. Perhaps Lo's model may be more efficient for screening, but it cannot be argued that the actual *in vivo* results, with tissue analysis, are less effective than an *ex vivo* model.

The Examiner also cites Chung *et al.* and Clari *et al.* as evidence that favorable results with therapeutic agents in experimental models have not been replicated in controlled clinical trials. Applicants respectfully submit that Chung *et al.* and Clari *et al.* are inapposite to the instant application. Chung *et al.* states that favorable results with therapeutic agents in experimental models of heart failure have frequently not been replicated in controlled clinical trials. (page 3138) However, the instant application is not related to heart failure. The therapeutic agent, the disease to be treated, and the physiological target of the treatment reported in Chung *et al.* are unrelated to the instant application. *In vitro* models for heart failure are also necessarily different from the *in vitro* model for neuronal cell growth. The correlation between *in vitro* models of one disease and the clinical condition of the disease, has no bearing on such correlation for a different disease. Accordingly, what is known in the field of art that pertains to Chung *et al.* and to the instant application is different and cannot be easily compared.

Even if the art is broadly defined to include both the instant application and the results of Chung *et al.*, the one instance of an unsuccessful trial represented by Chung *et al.* does not bear on the predictability of translation of *in vitro* data to the clinical use in general. Chung *et al.*, itself states that the agent, infliximab, has been shown to be an effective treatment for moderate to severe Crohn's disease and for active rheumatoid arthritis, in good correlation with *in vitro* results. The reported incongruity between the model system and the clinical trial results is but one unsuccessful happenstance among other more predictable results. Additionally, even if there

happens to be an inoperable embodiment that falls within the scope the claims, the presence of inoperable embodiments within the scope of a claim does not necessarily render a claim nonenabled. MPEP 2164.08(b). A showing of one negative result is not a conclusive evidence that other allegedly similar experiments will populate the genus and make the claim nonenabled.

Applicants have submitted data sufficient to show that there is a good correlation between the *in vitro* data and *in vivo* results in the particular field of claimed invention and provided adequate guidance for one skilled in the art to practice the invention as claimed. Applicants respectfully submit that these results amply demonstrate that Applicants' disclosures in the instant application fully enable practicing the invention.

35 USC §112, second paragraph - indefiniteness

Claims 1-12, 16-19, and 22-26 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-3, 8-12, 16-19, and 22-26 were rejected as indefinite for not having a step that clearly relates back to the preamble. The Examiner kindly suggested amendments to overcome this rejection. Without conceding the correctness of the Examiner's position, but to expedite prosecution of the subject application, Applicants have amended herein claims to incorporate the suggested language.

The Examiner also rejected claims 1-12, 16-19, and 22-26 as indefinite because they contain the term "morphogen activity," which the Examiner deems to be indefinite. Applicants respectfully draw the Examiner's attention to U.S. Application No. 08/445,467, now U.S. Patent 6,077,823 (the "'823 patent"), the disclosure of which is incorporated by reference into the instant application. In the '823 patent, Applicants disclosed:

> Specifically, the morphogens generally are capable of all of the following biological functions in a morphogenically permissive environment: stimulating proliferation of progenitor cells; stimulating the differentiation of progenitor cells; stimulating the proliferation of differentiated cells; and supporting the growth and maintenance of differentiated cells, including the "redifferentiation" of transformed cells.

(Column 18, lines 45-52). Applicants have also disclosed that:

> The morphogens described herein also can inhibit epithelial cell proliferation (see Example 10, below.)

(Column 18, lines 22-23). Thus, the activity of morphogen, or "morphogen activity," is clearly described in the specification by reference and thus, the claims are not indefinite.

The Examiner also rejected claims 1-12, 16-19, and 22-26 as indefinite because they contain the term "morphogen inhibition," which the Examiner considers to be indefinite. However, in view of the fact that "morphogen activity" is now shown herein to be clearly defined, it follows that "morphogen inhibition" is the inhibition of such activity. "Inhibition" is given an ordinary meaning that one skilled in the art would understand the word to mean.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Please charge our Deposit Account No. 18-1945, under Order No. JJJ-P01-569, for the requisite fee for two months extension from which the undersigned is authorized to draw. Applicants note that the subject application is entitled to small entity status as reflected on the corrected official filing receipt. Accordingly, even though fees have inadvertently been paid at the large entity rate, Applicants contend that the application was still entitled to small entity status. Accordingly, the fee for the extension of time is being paid at the small entity rate. Applicants believe no additional fees are due. However, if any fees are required, please charge our deposit account above for such additional fees.

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Respectfully submitted,

By _____

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